

Lead Exposure and Intelligence in 7-Year-old Children: The Yugoslavia Prospective Study

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For a prospective study of lead exposure and early development, we recruited pregnant women from a lead smelter town and from an unexposed town in Yugoslavia and followed their children through 7 years of age. In this paper we consider associations between lifetime lead exposure, estimated by the area under the blood lead (BPb) versus time curve (AUC7), and intelligence, with particular concern for identifying lead's behavioral signature. The Wechsler Intelligence Scales for Children-Version III (WISC-III) was administered to 309 7-year-old children, 261 of whom had complete data on intelligence, blood lead, and relevant sociodemographic covariates [i.e., Home Observation for the Measurement of the Environment (HOME), birth weight, gender, sibship size, and maternal age, ethnicity, intelligence, and education]. These showed anticipated associations with 7-year intelligence, explaining 41–47% of the variance in Full Scale, Performance, and Verbal IQ. Before covariate adjustment, AUC7 was unrelated to intelligence; after adjustment, AUC7 explained a significant 2.8%–4.2% of the variance in IQ. After adjustment, a change in lifetime BPb from 10 to 30 µg/dl related to an estimated decrease of 4.3 Full Scale IQ points; estimated decreases for Verbal and Performance IQ were 3.4 and 4.5 points, respectively. AUC7 was significantly and negatively related to three WISC-III factor scores: Freedom from Distractibility, Perceptual Organization, and Verbal Comprehension; the association with Perceptual Organization was the strongest. Consistent with previous studies, the IQ/lead association is small relative to more powerful social factors. Findings offer support for lead's behavioral signature: perceptual-motor skills are significantly more sensitive to lead exposure than are the language-related aspects of intelligence. *Key words:* child development, intelligence, lead, perceptual motor functioning, WISC-III.

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A series of prospective studies in diverse communities suggests that exposure to environmental lead is associated with small decreases in intellectual functioning in childhood (1–4), even after control for sociodemographic conditions that are associated with both exposure and lower developmental scores. Whether these decrements persist in the school years is of particular importance because they are likely to have the most salient impact for children in the school setting.

In the Port Pirie prospective study of children residing in a smelter town, cumulative exposure, estimated by lifetime average blood lead, was negatively associated with Wechsler Intelligence Scale for Children-Revised (WISC-R) Full Scale IQ at ages 7–8 years, even after control for sociodemographic confounders (5). Depending on the age at which blood lead concentration (BPb) was examined, an increase from 10 to 30 µg/dl was associated with a 4–7 point decrement in covariate-adjusted IQ scores. In another report from Port Pirie (6) in which cumulative exposure was estimated by lead

levels in shed teeth, an increase in dentine lead from 3 to 22 ppm was associated with a decline in covariate-adjusted WISC-R Full Scale IQ of 5.1 points.

Similar results have been reported for cohorts in Cincinnati, Ohio, and Boston, Massachusetts. In Cincinnati, mean BPb concentrations in children at 5 and 6 years of age (but not earlier) were associated with lower WISC-R Full Scale IQ scores at 6.5 years (7), even after covariate adjustment. In Boston, 2-year BPb levels were significantly associated with lower covariate-adjusted WISC-R Full Scale IQ scores at 10 years of age (8), although BPb measured at other time points was not consistently related to developmental scores. A 10 µg/dl increase in 2-year BPb resulted in a 5.8 point decrease in subsequent IQ.

While these studies rather consistently link lead exposure to small decreases in intellectual functioning, it is still not clear whether there is a particular behavioral signature (9) for lead. In this context, four prospective studies of lead exposure note that preschool perceptual-motor functioning

is particularly sensitive to exposure. The Port Pirie (10), Boston (11), and Yugoslavia (1) studies reported strongest associations between BPb and the McCarthy Scales of Children's Abilities (MSCA) Perceptual-Performance subscale in 4-year-old children. The Cincinnati study reported a correspondingly stronger adverse impact of BPb on 5 year intelligence on the Kaufman Assessment Battery for Children (K-ABC) Simultaneous Processing subscale.

Recent work concerning motor development also suggests that exposure to lead may affect visual-motor integration. For example, in Port Pirie children at 7 years of age, both prenatal and postnatal Pb exposure were adversely associated with functioning on the Beery Test of Visual-Motor Integration (VMI) (12). In Cincinnati in 6-year-old children (13), postnatal BPb was associated with poorer functioning on those subtests of the Bruininks-Oseretsky Test of Motor Proficiency that reflect similar visual-motor skills (visual-motor control, upper limb speed and dexterity, fine motor composite).

More fine-grained examinations of WISC subscale scores in school-age children also suggest an association between lead exposure and problems in visual-motor functioning. In Port Pirie children at 7 years of age, two separate reports link lifetime average BPb concentration (5) and tooth lead concentration (6) to certain WISC-R subscales. In Boston, BPb in 2-year-old children also showed adverse associations with particular WISC-R subscales at age 10 years (14). Despite differences across studies in which WISC subscales are most sensitive to lead exposure, the Block Design subtest is associated with lead exposure in all three. This subtest requires the child to manually reproduce with blocks a picture of a visually presented pattern. It is noteworthy that this is the same function assessed on the VMI

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and on many of the subcomponents of the MSCA Perceptual-Performance subscale, both of which have also been found to be particularly sensitive to lead effects.

Factor analysis of the WISC-R subscales consistently yields three factors: Perceptual Organization, Verbal Comprehension, and Freedom from Distractibility (15). Perceptual Organization is another measure of visual-motor integration. In Boston (14), after covariate adjustment, postnatal BPb was not significantly related to either Perceptual Organization or to the Verbal Comprehension factor, although it was negatively related to scores on the Freedom from Distractibility factor in 10-year-olds. The latter taps a range of skills, including planning ability and distractibility (16), and is found to be significantly lower in children with attention-deficit hyperactivity disorder (ADHD) (17–19). Thus, this observation is consistent with clinical reports of problems in attention and distractibility in lead-exposed children (20–22).

The Yugoslavia Prospective Study, which has the widest range of Pb exposure and socioeconomic status of all such studies, is chronologically the last of the major prospective studies that examine the consequences of prenatal and postnatal Pb exposure. In the present paper, we test the hypotheses that Pb exposure is related adversely to intelligence in school-aged children and that associations are strongest with visual-motor functioning and Freedom from Distractibility.

Methods

The study was conducted in two towns in Kosovo, Yugoslavia. Kosovska Mitrovica is the site of a lead smelter, refinery, and battery factory; Pristina is a nonexposed town 25 miles to the south. Our sample was selected for follow-up from a prospective study of 1,502 pregnant women living in those towns in 1984–1985. Pregnancy outcomes (23,24) and developmental outcomes at ages 2 and 4 years (1,2) have been described earlier. The pregnancy study was initiated in 1985; the assessments described here occurred between October 1990 and April 1994. Hostilities began in Croatia and Bosnia late in 1991; although these events were far distant from Kosovo, during the course of data collection, Kosovo suffered the economic consequences of the United Nations embargo of Serbia that began in the spring of 1992.

Subjects. Details of the study and sample selection for the prospective study have been previously described (2). Briefly, 706 infants were invited to participate in a follow-up study involving visits at 6-month

intervals. Of these, the parents of 577 children consented and brought the child to one or more visits by age 7.5 years.

The present analyses consider assessments of intellectual functioning at ages 5 and 7 years. Of those who consented, 318 children were seen for their 5-year visit. Two hundred fifty-six children were seen for a subsequent wave of cognitive testing at 6.5 years; of those not tested at 6.5 years, an additional 35 and 18 children, respectively, were evaluated at 7.0 and 7.5 years. Data from these 309 children evaluated at 6.5, 7.0, or 7.5 years of age, were consolidated and are referred to below as having been seen at age 7.

Procedure. At midpregnancy, delivery, and at subsequent 6-month intervals, venous blood samples were taken for measuring BPb (25), erythrocyte protoporphyrin (EP) (26), serum ferritin (SF) (27), and hemoglobin (Hgb). Whole blood samples were appropriately stored and transported to Columbia University, where the laboratory participates in the BPb and EP quality control program of the Centers for Disease Control and Prevention. During the period from October 1990 through April 1994, agreements with the quality control values for both BPb and EP, measured by intraclass correlation coefficients, were 0.998. All interviews and assessment instruments were translated and administered in the two dominant languages of the region, Serbo-Croatian and Albanian. Weight, height, and head circumference were recorded at each visit. Mothers were interviewed regularly about child and family health, diet, and demographics.

Measures. Child intelligence at 5 and 7 years of age was assessed by the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) and Wechsler Intelligence Scale for Children-Version III (WISC-III), respectively, each translated into the Albanian and Serbian languages. These are two age versions of closely related individually administered tests. Each has recently been restandardized and each shows good reliability and validity.

The WISC-III, suitable for children age 6 years and older, consists of five (or six, depending upon administration) verbal subtests that together provide a Verbal IQ score, and a similar number of performance subtests that together provide a Performance IQ score (19). We administered five verbal subtests: Information, Similarities, Arithmetic, Comprehension, and Digit Span. Translated vocabulary items often have different secondary meanings in different languages. Thus, we chose not to administer the Vocabulary subtest, substituting Digit Span instead. The five performance subtests

included Picture Completion, Coding, Picture Arrangement, Block Design, and Object Assembly.

In addition to Full Scale, Performance, and Verbal IQ, the WISC-III provides four factor scores, as compared to the three factors generated by the older WISC-R (19,28). We calculated three factor scores of interest: Perceptual Organization, Verbal Comprehension, and Freedom from Distractibility. The Perceptual Organization factor is the sum of scaled scores for Picture Completion, Picture Arrangement, Block Design, and Object Assembly. The Freedom from Distractibility factor is the sum of scaled scores for Digit Span and Arithmetic subtests. Because we had not administered the Vocabulary subtest, we calculated Verbal Comprehension from the remaining component subtests (i.e., the scaled scores for Comprehension, Similarities, and Information were summed and multiplied by 1.33).

The WPPSI-R, standardized on U.S. children between 3 and 7 years of age, includes five verbal and five performance subscales (29). We examined Full Scale, Performance, and Verbal IQ.

An adaptation of the preschool version of the Home Observation for Measurement of the Environment [HOME (30)], in structured interview format, was administered to each family when children were approximately 3 years of age during a home visit to assess the quality of the childrearing environment. This measure is widely used as a predictor of child intelligence and achievement (31). The total score was used in the present analyses.

Maternal intelligence was assessed with Raven's Standard Progressive Matrices (32), a nonverbal test relatively free of cultural influences.

BPb levels measured at intervals close in time (e.g., at 6-month intervals) are highly correlated, making analyses using each separate age assessment of BPb redundant. For this reason, we defined *a priori* three developmental intervals for which cumulative exposure could be estimated (1). For the present report, these intervals were birth to 2 years, 2–4 years, and 4–7 years of age. Cumulative lifetime exposure during each designated interval was estimated using trapezoidal approximation of area under the log₁₀ BPb curve (AUC). These calculations were only made if BPb was available for the start and end of that interval. [For analyses predicting WISC-III scores at age 7, we used the age at which the IQ test was administered (6.5–7.5 years) as the final point in calculating lifetime exposure. For 12 children lacking an assessment of BPb at that age, we used the BPb collected at the prior

visit (6 months earlier)]. For example, the AUC measure from 2 years through 4 years of age was calculated for those children with actual BPb data at ages 2 and 4 years, even if one or more of the intervening assessments were missing. The cross-age correlations for the AUC measures showed considerable stability (average $r = 0.80$), rendering uninformative comparisons of associations with lead level at different age intervals. We therefore estimated lifetime lead exposure with a single cumulative measure through age 7 (AUC7) or age 5 (AUC5).

Missing data. Analyses computing Verbal or Performance IQ required four of five offered tests to be completed; analyses computing Full Scale IQ required that both Verbal and Performance IQ first be determined. Among 309 children administered the WISC-III at age 7, 6 children were excluded from one or another of the analyses because of incomplete tests. Analyses examining Verbal and Performance IQ and factor scores made use of all available subjects, even if they lacked complete data for calculation of some other score. Among the 318 children tested at 5 years of age with the WPPSI-R, 3 children were excluded from various analyses because of incomplete tests.

Of the 309 children tested at age 7, 16 were excluded from analyses because they were missing data on one or more of the covariates, including 1 child who was excluded because of an incomplete WISC-III.

For 32 of the 309 children administered the WISC-III at 7 years of age, an insufficient number of serial BPb assessments were available for calculating AUC7; thus, these children were dropped from further analyses.

Statistical analyses. Ordinary least squares regression analysis was used to estimate associations between cumulative Pb exposure through age 7 (AUC7) and 7-year IQ. BPb was log-transformed (\log_{10}) in all analyses because its distribution is skewed. We first examined the 7-year IQ scores as the outcome variables and then repeated the analyses for the WPPSI-R IQ, measured at age 5 years.

Regression models included several covariates that were chosen, in part, to facilitate comparisons with other published studies. Covariates included gender, sibship size at the time of the IQ test, birth weight, language spoken in the home (as a marker for ethnicity: Serbian, Albanian, other), HOME score, years of maternal education, maternal age, and maternal Raven's test score. For each analysis we estimated the association between BPb and IQ, both before and after adjusting for this set of covariates. In our earlier work, iron status was an important contributor to 2-year

Table 1. Sample characteristics of children at 7 years of age

	Not assessed at age 7 ^a (towns combined; $n = 268$)	Assessed at age 7 ^a (towns combined; $n = 309$)	Assessed at age 7 ^b (Pristina only; $n = 153$)	Assessed at age 7 ^b (Mitrovica only; $n = 156$)
Mitrovica (%)	60.4 ^{c*}	50.5		
Pristina (%)	39.6	49.5		
Sex (% male)	56.0	50.2	48.4	51.9
Ethnicity				
Albanian (%)	48.7 ^{c**}	61.4	71.9 ^{d*}	56.4
Serbian (%)	32.8	29.4	23.5	35.3
Other (%)	18.5	6.5	4.6	8.3
Birth weight (g)	3,356 (504)	3,336 (512)	3,332 (484)	3,340 (540)
Maternal education (years)	9.3 (4.0)	9.2 (3.8)	9.1 (3.9)	9.4 (3.8)
Sibship size	—	3.2 (1.5)	3.4 (1.5) ^{d*}	3.0 (1.5)
Maternal IQ	31.5 (13.7)	32.7 (12.5)	30.7 (12.8) ^{d**}	34.8 (11.8)
HOME score	28.1 (8.1)	30.2 (7.3)	29.2 (7.6) ^{d*}	31.3 (7.0)
Age 7 BPb	—	21.2 (15.4)	8.0 (3.1) ^{d*}	34.0 (11.0)
Cumulative BPb (AUC7)	—	1.21 (0.34)	0.87 (0.11) ^{d*}	1.52 (0.12)
Midpregnancy BPb	13.0 (8.4)	13.3 (9.6)	5.6 (2.0) ^{d*}	20.8 (7.9)
Umbilical cord BPb	14.5 (9.6)	14.5 (10.8)	5.7 (3.6) ^{d*}	23.2 (8.2)
Midpregnancy Hgb	12.4 (1.2)	12.4 (1.1)	12.3 (1.2)	12.4 (1.1)
Umbilical cord Hgb	16.0 (2.6)	16.1 (2.1)	16.4 (2.1)	15.9 (2.0)

Abbreviations: HOME, Home Observation for the Measurement of the Environment; AUC7, area under the blood Pb \times time curve at age 7 years; BPb, blood lead concentration; Hgb, hemoglobin concentration. Standard deviation is shown in parentheses.

^aIncludes those with missing data on some measures.

^bIncludes only those with complete data.

^cDifference between assessed/not assessed at age 7 is significant.

^dDifference between towns is significant.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

developmental functioning (2); therefore, all analyses were repeated, adjusting for hemoglobin concentration at 7 years of age.

Analyses estimating the association between BPb and Freedom from Distractibility, Perceptual Organization, and Verbal Comprehension were adjusted for the same set of covariates. A multivariate test was performed to test the hypothesis that the coefficients for AUC7 for Perceptual Organization and Verbal Comprehension were the same (33).

Results

Sample characteristics. Children not assessed at age 7 years were significantly more likely to be from Mitrovica [$\chi^2(1, n = 569) = 5.59$; $p < 0.01$] and Serbian [$\chi^2(2, n = 568) = 11.87$; $p < 0.005$] (Table 1).

Compared to children assessed at 5 years of age, those not assessed had higher scores on the HOME and their mothers had higher Raven's scores. Those not assessed were more likely to be from Mitrovica, and their available earlier measures of BPb (midpregnancy and cord) were correspondingly higher than those not assessed (data not shown).

Among children seen at age 7, those from Mitrovica were significantly more likely to be Albanian rather than Serbian [$\chi^2(2, n = 309) = 8.18$; $p < 0.02$] and had significantly fewer siblings [$t(307) = 2.04$; $p < 0.05$] (Table 1). As expected, all BPb measures were significantly higher in Mitrovica. Finally, mothers from Mitrovica had significantly higher maternal IQ (Raven) [$t(301) = 2.87$; $p < 0.005$] and HOME [$t(297) = 2.50$; $p < 0.05$] scores.

Hematologic findings. Mean values for BPb, EP, hemoglobin concentration (Hgb), and serum ferritin concentration (SF) are plotted against age in Figure 1. In Mitrovica, BPb rose continuously through the second year of life; EP also rose through age 2 and then gradually declined. A similar pattern for BPb and EP was found for Pristina, although with much smaller rises. In Mitrovica, after age 2, BPb remained rather constant while EP gradually declined. No differences were observed between towns for either ferritin or Hgb.

Associations with covariates. Where possible, regression analyses considered covariates as continuous measures. For descriptive purposes, however, Table 2

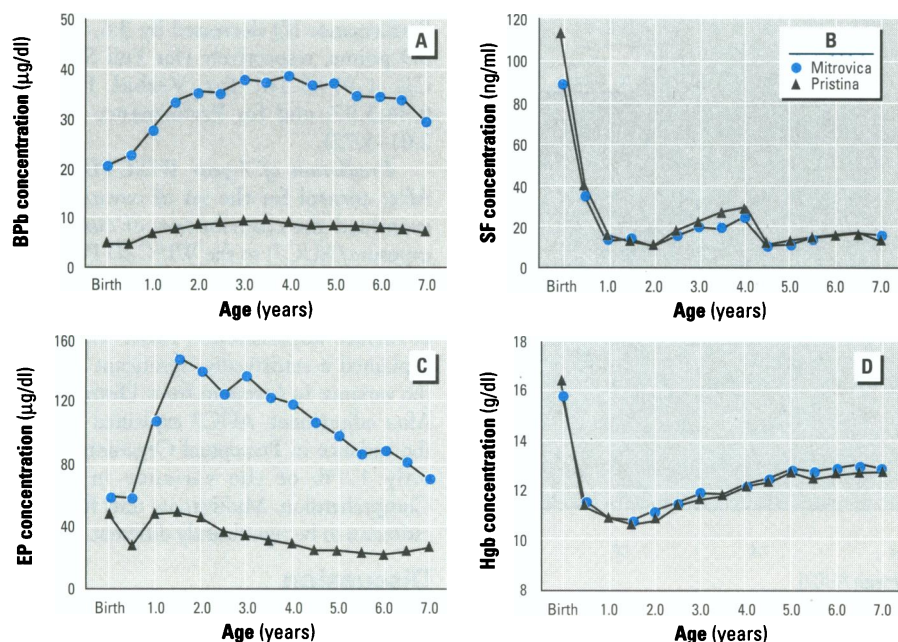


Figure 1. Hematologic findings for children who were assessed at 7 years of age. (A) Geometric mean blood lead (BPb) concentrations; (B) Geometric mean serum ferritin (SF) concentrations; (C) Geometric mean erythrocyte protoporphyrin (EP) concentrations; (D) Arithmetic mean hemoglobin concentrations (Hgb).

shows univariate associations between strata of covariates and intelligence at 7 years of age. Associations between Full Scale, Verbal, and Performance IQ were in the expected direction. Intelligence decreased as sibship size increased and as birth weight, maternal intelligence, maternal education, maternal age, and HOME scores increased. Intelligence scores were higher in children of Serbian ethnicity.

Effects of cumulative exposure with and without covariate adjustment. Before covariate adjustment, cumulative exposure (AUC7) was not associated with 7-year Full Scale, Performance, or Verbal IQ (Table 3). Unadjusted associations ranged from $\beta = -0.05$ for Verbal IQ to $\beta = -0.08$

for Performance IQ. Hgb was also not significantly associated with either 5- or 7-year IQ, and the addition of Hgb did not change the estimate of the Pb parameters. Therefore, analyses are presented without Hgb in the model.

Adjustment for covariates, however, clarifies the subtle nature of the association between BPb and intelligence. Table 3 presents regression analyses predicting 7-year Full Scale, Verbal, and Performance IQ with lifetime cumulative lead exposure (AUC7) in the model. The quality of the HOME and ethnicity accounted for the largest portion of the variance in 7-year Full Scale, Performance, and Verbal IQ, with values ranging between 26 and 30%

Table 2. Relationships between covariates and 7-year IQ

Covariate	Full scale IQ (n = 303 ^a)	Performance IQ (n = 307 ^a)	Verbal IQ (n = 305 ^a)
Sibship size			
1	77.90	77.85	81.50
2	79.70	79.78	82.73
3	75.92	75.59	80.04
4	73.32	73.15	77.10
5+	68.04	67.33	73.22
Raven's			
9–21	69.03	68.70	74.04
22–33	72.48	72.37	76.40
34–43	77.09	76.36	81.52
44–60	83.72	84.04	85.77
Maternal education (years)			
<8	67.95	68.32	72.07
8–11	71.31	70.91	75.99
12+	81.58	81.28	84.75
HOME			
7–24	67.14	66.97	71.75
25–30	72.54	72.65	76.82
31–34	78.13	77.74	81.83
35–39	83.77	83.40	86.78
Birth weight (g)			
1,750–3,040	71.36	70.64	76.20
3,041–3,350	76.27	76.74	79.67
3,351–3,650	76.43	75.57	80.51
3,651–4,600	78.11	78.08	81.19
Ethnicity			
Albanian	72.52	72.53	76.62
Serbian	82.96	81.99	86.49
Other	71.19	71.32	74.29
Gender			
Male	75.92	75.55	79.97
Female	75.16	74.97	78.82
Maternal age (years)			
16.0–22.7	72.68	72.41	77.14
22.8–25.8	74.11	74.04	77.77
25.9–29.6	78.83	78.19	82.37
29.7–32.0	79.69	76.55	80.36

Abbreviations: HOME, Home Observation for Measurement of the Environment; Raven's, Raven's Standard Progressive Matrices.

^aIncludes those with missing data on some measures.

Table 3. Associations between IQ, covariates, and AUC7

Measure	Full Scale IQ (n = 258)		Performance IQ (n = 261)		Verbal IQ (n = 259)	
	Est $\beta \pm$ SE	β	Est $\beta \pm$ SE	β	Est $\beta \pm$ SE	β
HOME score	0.6514 \pm 0.1052	0.3425 [#]	0.5993 \pm 0.1149	0.3086 [#]	0.6037 \pm 0.1038	0.3398 [#]
Serbian	7.9737 \pm 1.5339	0.2606 [#]	6.6050 \pm 1.6814	0.2051 [#]	7.9227 \pm 1.5128	0.2773 [#]
Other	6.1233 \pm 2.8031	0.1024 [*]	8.0809 \pm 2.8635	0.1404 ^{**}	3.1339 \pm 2.6758	0.0580
Mother's age	0.5913 \pm 0.1283	0.2199 [#]	0.6403 \pm 0.1412	0.2271 [#]	0.4650 \pm 0.1260	0.1856 [#]
Birth weight (kg)	3.8645 \pm 1.2050	0.1483 [#]	4.3638 \pm 1.3178	0.1607 ^{**}	2.6721 \pm 1.1885	0.1097 [*]
Raven's	0.2019 \pm 0.0585	0.1852 [#]	0.2065 \pm 0.0639	0.1808 ^{**}	0.1498 \pm 0.0576	0.1472 ^{**}
Mother's education	0.4584 \pm 0.2041	0.1291 [*]	0.4478 \pm 0.2231	0.1224 [*]	0.4515 \pm 0.2007	0.1364 [*]
Sibsize	-0.6683 \pm 0.5274	-0.0721	-1.2457 \pm 0.5617	-0.1346 [*]	-0.1603 \pm 0.5201	-0.0185
Gender (0 = boy)	-0.1766 \pm 1.2562	-0.0065	0.6207 \pm 1.3787	0.0218	-0.9674 \pm 1.2363	-0.0383
Mean AUC7	-8.5864 \pm 1.8868	-0.2146 [#]	-9.1669 \pm 2.0659	-0.2177 [#]	-6.5931 \pm 1.8611	-0.1765 [#]
Mean AUC7 (unadjusted)	-2.8998 \pm 2.4946	-0.0725	-3.2524 \pm 2.6083	-0.0773	-1.7773 \pm 2.3281	-0.0476

Abbreviations: AUC 7, area under the blood Pb \times time curve at age 7 years; HOME, Home Observation for the Measurement of the Environment; Est β , estimated regression coefficient; β , standardized regression coefficient; SE, standard error; Raven's, Raven's Standard Progressive Matrices.

^{*} $p < 0.05$; ^{**} $p < 0.01$; [#] $p < 0.001$.

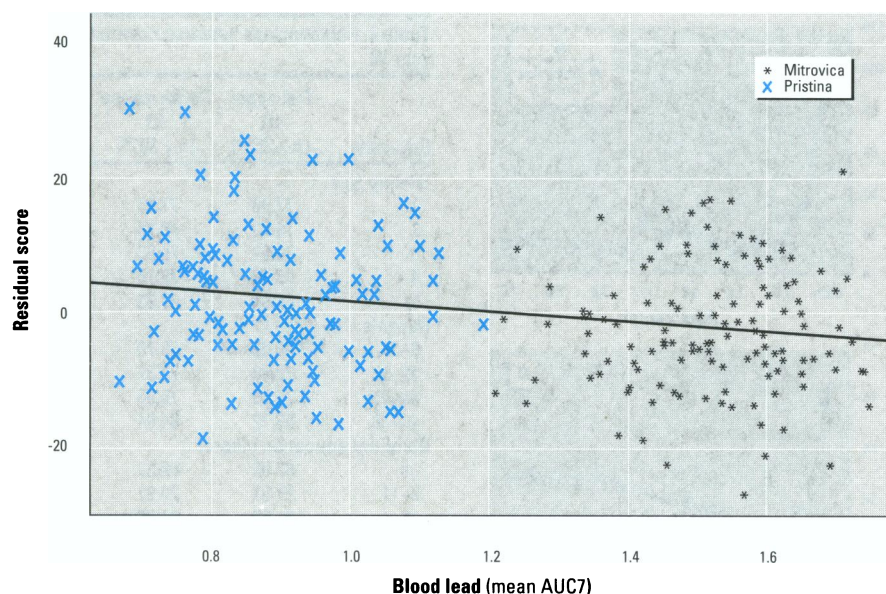


Figure 2. Covariate-adjusted Full Scale IQ (residual scores) across levels of cumulative lead exposure. AUC7, area under the blood lead \times time curve at age 7 years.

for HOME and between 4.1 and 6.3% for ethnicity. Children living in more adequate homes (higher HOME score) and those of Serbian ethnicity had significantly higher 7-year intelligence scores. Children of older and more educated and intelligent mothers had significantly higher IQ scores at age 7, as did those whose birth weights were higher. Neither child sex nor sibship size made significant contributions to 7-year IQ when other covariates were taken into consideration. Taken altogether, these covariates explained approximately 44–50% of the variance in Full Scale, Performance, and Verbal IQ.

After covariate adjustment, AUC7 was significantly and negatively associated with Full Scale, Performance, and Verbal IQ (Table 3), explaining 4.2, 4.3, and 2.8%, respectively, of the variance in these measures. After covariate adjustment, a change in lifetime BPb from 10 to 30 $\mu\text{g}/\text{dl}$ was associated with an estimated decrease of 4.3 points [95% confidence intervals (CI), 3.4–5.1] in Full Scale IQ; corresponding estimated decreases for Verbal and

Performance IQ were 3.4 (CI, 1.7–5.0) and 4.5 points (CI, 2.7–6.3), respectively.

Residual scores for Full Scale, Verbal, and Performance IQ, adjusted for the set of covariates and plotted against AUC7, showed relatively linear dose–response associations that spanned the range of BPb concentrations. Full Scale IQ is plotted in Figure 2; patterns were similar for Verbal and Performance IQ. In Figure 2, scores for Pristina cluster on the left and those for Mitrovica cluster on the right.

Analyses predicting 5-year IQ. Similar results (not shown) were obtained from the analysis of 5-year intelligence. Before covariate adjustment, AUC5 was not associated with measures of child intelligence. The set of sociodemographic covariates explained between 40 and 48% of the variance in measures of intelligence. After covariate adjustment, all three regression coefficients for AUC5 increased, with lead accounting for 3.6, 3.5, and 2.1% of the variance in Full Scale, Performance, and Verbal IQ, respectively ($p < 0.005$). As mean lifetime BPb rose from 10 to 30 $\mu\text{g}/\text{dl}$, we

estimate that 5-year Full Scale, Verbal, and Performance IQ decreased by 3.6, 2.4, and 3.9 points, respectively (for Full Scale IQ, CI, 1.97–5.16; for Verbal IQ, CI, 0.94, 3.97; and for Performance IQ, CI, 2.01–5.72).

Prediction of 7-year WISC-III factors.

After control for the set of covariates, we examined the contribution of cumulative exposure (AUC7) to the WISC-III Perceptual Organization, Verbal Comprehension, and Freedom from Distractibility factors. After covariate adjustment (Table 4), AUC7 explained a statistically significant 2.5% of the variance in Freedom from Distractibility. After adjustment, AUC7 explained 5.3% of the variance in Perceptual Organization, but only 1.7% of the variance in Verbal Comprehension. Multivariate tests found the estimates to be significantly different.

Discussion

We found a small but statistically significant adverse impact of BPb on school age Full Scale, Verbal, and Performance IQ; this result is consistent with those of others [e.g., (5,7,8)]. In the same cohort, we have previously described associations of similar magnitude of effects on infant developmental scores (Bayley Scales) at 2 years of age (2), and on IQ (MSCA) at ages 3 and 4 years (1). Thus, despite an increase in cumulative exposure, maturation, and a change in the test used, the strength of the lead–intelligence association is remarkably consistent.

Among the numerous strengths of the present investigation are the length of follow-up, the broad range of both exposures and social factors, and the opportunity to replicate the work of others in a different cultural context. A limitation is the relatively high rate of loss to follow-up (45% of the recruited sample). To some degree, this reflects the difficulties in conducting a longitudinal study in a setting characterized by ethnic strife.

As in other studies, we find the adverse impact of BPb on IQ to be small in comparison to the more substantial impact of sociodemographic variables. For example, in the current analyses, the quality of the HOME, measured at ages 3–4 years, explained 25–30% of

Table 4. Associations between AUC7 and WISC-III factor scores, before and after covariate adjustment

	Freedom from Distractibility (<i>n</i> = 258)		Perceptual Organization (<i>n</i> = 253)		Verbal Comprehension (<i>n</i> = 257)	
	Est $\beta \pm$ SE	β	Est $\beta \pm$ SE	β	Est $\beta \pm$ SE	β
Mean AUC7 (unadjusted)	-2.7686 \pm 3.2953	-0.0524	-4.2669 \pm 2.6458	-0.1013	-0.5810 \pm 2.0313	-0.0179
Mean AUC7 (adjusted)	-8.7952 \pm 2.8408	-0.1666**	-10.1340 \pm 2.0509	-0.2405***	-4.4100 \pm 1.7028	-0.1359*

Abbreviations: AUC7, area under the blood Pb \times time curve at age 7 years; WISC-III, Wechsler Intelligence Scale for Children-Version III; Est β , estimated regression coefficient; β , standardized regression coefficient.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

the variance in 7-year IQ, compared to the 2–4% explained by BPb.

The present findings offer further support for the idea that lead may have a behavioral signature (9) more closely linked to some functions than to others. Earlier, we (1) and others (34) have suggested that visual-spatial tasks are especially sensitive to lead exposure, both in children and in animals. Neurochemical evidence suggests that the hippocampus, which plays a central role in both spatial learning and in the planning of sequences (35), is a site that accumulates lead in animals (36–38) and in humans (39). In particular, the strongest associations with lead were found with the Perceptual Organization factor, while lead was less strongly associated with the Verbal Comprehension factor, even after covariate adjustment.

One other report examined associations between WISC-R factors and BPb (14). While that report noted no significant associations between BPb and either the Verbal Comprehension or Perceptual Organization factor, it did note a significant adverse association between postnatal (24-month) BPb and the Freedom from Distractibility factor. In the present investigation, we also found a significant adverse association between postnatal BPb and the Freedom from Distractibility factor, perhaps reflecting difficulties in the management of attention.

The actual interpretation of the significance of the Freedom from Distractibility factor is somewhat controversial (16). The factor may reflect the mental processes used in planning, processes that reflect the sequencing of actions, or processes that underlie resistance to distractions. Early clinical studies noted an increased likelihood of symptoms of ADHD (20,21) in lead-exposed children, although more recent systematic studies find such associations to be very small (40–42), and lead has not been linked to the full clinical disorder of ADHD. Nonetheless, children with ADHD do indeed often score more poorly on Freedom from Distractibility. The inconsistency in reports of a Pb–ADHD connection may therefore reflect underlying problems in both lead-exposed and ADHD children in the planning and sequencing of actions. These underlying planning and sequencing deficits may account for the phenotypic correspondence between the sequelae of lead exposure and ADHD.

In conclusion, we find small but statistically significant adverse associations between environmental Pb exposure and intelligence in school-aged children. Cognitive functions that relate to perceptual organization and to resistance to distractions seem to be more

negatively affected by lead exposure than are other functions, such as language comprehension. These associations were not apparent until sociodemographic covariates were controlled, indicating that in the present sample, these variables suppress the associations between Pb and intelligence. Indeed, despite the wide differences in exposure levels between the two towns studied, the unadjusted mean IQ scores of the children were virtually identical. We thus conclude that there are subtle effects of environmental Pb exposure on intelligence, but that the effects of social circumstances are substantially greater.

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Objectives:

To identify and discuss recent advances in food science and technology that may impact the food supply in Asia.
To provide a forum for discussion of future directions in food safety and nutrition among scientists from academia, government, and industry.
To examine scientific factors that limit or promote the harmonization of food safety regulations within the region.
To review the impact of various factors, including the work of the World Trade Organization and the Sanitary and Phyto-Sanitary Measures, on the development of regulations to ensure the safety and availability of foods within the region.
To examine nutritional issues important for Asian populations including fortification, food-based dietary guidelines, and the scientific basis for health benefits of functional foods.

Proposals for oral or poster presentations within the defined topic areas are being solicited and should be submitted before December 1, 1997.